PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for CONCERTA (Methylphenidate Hydrochloride)

This is a summary of the Risk Management Plan (RMP) for CONCERTA. The RMP details important risks of CONCERTA, how these risks can be minimized, and how more information will be obtained about CONCERTA's risks and uncertainties (missing information).

CONCERTA's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how CONCERTA should be used.

Important new concerns or changes to the current ones will be included in updates of CONCERTA's RMP.

I. The Medicine and What it is Used For

CONCERTA is authorized for attention deficit hyperactivity disorder (ADHD) (see SmPC for the full indication). It contains methylphenidate hydrochloride as the active substance and it is given orally by prolonged-release tablets.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of CONCERTA, together with measures to minimize such risks and the proposed studies for learning more about CONCERTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CONCERTA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CONCERTA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of CONCERTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CONCERTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important Identified Risks	• Serious cardiovascular events • Psychosis/mania • Verbal or motoric tics • Depression • Aggression • Drug abuse/Drug dependence • Withdrawal syndrome • Reduced weight gain • Decreased rate of growth • Seizures • Cerebrovascular disorders
Important Potential Risks	• Suicidality • Sexual maturation delayed
Missing Information	• Long-term effects

II.B. Summary of Important Risks

The safety information in the Product Information is aligned to the reference medicinal product.

Important Identified Risk: Serious cardiovascular events	
Evidence for linking the risk to the medicine	Cases of serious cardiovascular events have been reported in pediatric clinical trials and the postmarketing setting, and cases of sudden death have also been reported in the postmarketing setting. Cardiovascular events also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	General risk factors for hypertension in children include being overweight or obese, family history of high blood pressure, type 2 diabetes or a high fasting blood sugar level, and high cholesterol and triglycerides (Mayo Clinic, 2012a). Long QT syndrome can be inherited and is also more common in children who are born deaf. In boys, the QT intervals often return toward normal after puberty (National Heart, Lung, and Blood Institute, 2013). In addition, children and teenagers who experience unexplained fainting, near drownings, or other accidents, and unexplained seizures may also be at risk. Medications known to prolong QT intervals, and eating disorders, such as anorexia, can also contribute to increased risk (Mayo Clinic, 2012b). Causes of arrhythmias (including tachycardias) in children include cardiomyopathy or congenital heart disease. Other common causes are infections, chemical imbalances, fever, and certain medications (Cleveland Clinic, 2011). Atrial tachyarrhythmias are most commonly seen in children with congenital heart disease in whom cardiac surgery has been performed. According to a German study (Grosse-Wortmann et al, 2010) of 494 neonates and older children during first 72 hours after surgery for congenital heart disease found that for neonates, male sex and longer cross-clamping time independently increased risk for arrhythmias. Ventricular septal defect repair was a strong risk factor for junctional ectopic tachycardia in neonates and in older children. Finally, older age and closure of atrial septic defects predisposed infants and children to arrhythmias of any type. Risk factors for ischemic cardiac events include physical inactivity, smoking, high blood cholesterol and other lipids, high blood pressure, diet, excess weight and obesity, and diabetes mellitus (Lloyd-Jones et al, 2010). Risk factors in children include a history of familial hypercholesterolemia and a family history of early coronary heart disease (Dadfarmay and Dixon, 2009). Long-standing hypertension and myocardial infarction (ischemic myopathy) are known risk factors for developing cardiomyopathy. Literature per Cooper et al (Cooper et al, 2011) concluded that among young and middle-aged adults (ages 25 to 64 years) current or new use of ADHD medication was not associated with an increased risk of Serious cardiovascular events. However, hypertensive heart disease (or long-standing hypertension) can manifest as left ventricular hypertrophy with isolated diastolic

	dysfunction and preserved systolic function. Due to remodeling over time, the hypertrophy can progress to a dilated cardiomyopathy with systolic dysfunction. Although hypertrophic cardiomyopathy is usually inherited, it can also develop from long standing hypertension. Patients who are using CONCERTA long term into adulthood could have a risk of developing high blood pressure, and/or myocardial infarction, therein also theoretically having a potential risk of developing cardiomyopathy. The incidence rates for sudden cardiac death and sudden unexpected death increase with age and they were found to be higher in boys/men than girls/women in all age groups and populations. Known risk factors for cardiovascular disease include cigarette smoking, hypertension, physical inactivity, obesity, dyslipidemia, hyperinsulinemia, homocysteinemia, and poor nutrition. ADHD has not been identified as a risk factor in sudden death. However, it is believed that patients with structural cardiac abnormalities may be at a greater risk of sudden death when treated with CONCERTA. For instance, a matched case-control study investigating 564 cases of sudden death occurring at ages 7 to 19 years across the United States matched to 564 subjects dying in motor vehicle accidents observed that 1.8% of sudden deaths were in youths taking stimulants compared to 0.4% in the control group. Hence, a significant association of stimulant use with sudden death was concluded based on exact conditional logistic regression (odds ratio 7.4; 95% confidence interval: 1.4 to 74.9) (Gould et al, 2009).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Additional pharmacovigilance activities	• Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) studies
Important Identified Risk: Psychosis/Mania	
Evidence for linking the risk to the medicine	Cases of psychosis/mania have been reported in pediatric clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA

Risk factors and risk groups	Data from controlled trials and postmarketing surveillance on ADHD drugs in the pediatric population found psychosis/mania events in children exposed to ADHD drugs while no comparable events occurred with placebo exposure (Mosholder et al, 2009). A prospective nationally representative cohort study from the United Kingdom involving over 2,200 twelve-year-old children followed up since age 5 years also identified potential risk factors for children's psychotic symptoms to include familial and heritable factors; social risk factors (eg, urbanicity); cognitive impairments at age 5; home-rearing risk factors (eg, maternal expressed emotion); behavioral (eg, ADHD symptoms), emotional, and educational problems at young age; and comorbid conditions such as self-harm, symptoms of depression, and anxiety (Polanczyk et al, 2010). Potential risk factors for non-psychotic auditory hallucinations in children and adolescents could include personal and family stresses, change of school, admission to hospital, actual or threatened separation from parents and loss of friends or relatives through death, in addition to higher rate of a positive family history of psychosis and depression (Perera et al, 2011; Yates and Bannard, 1988; Burke et al, 1985).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Verbal or motoric tics	
Evidence for linking the risk to the medicine	Cases of verbal or motoric tics have been reported in pediatric clinical trials and the postmarketing setting and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	The Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2014a) summarized that genetic studies have indicated that Tourette's syndrome is inherited as a dominant gene, with about 50% chance of parents passing gene on to their children; boys with the gene are 3 to 4 times more likely than girls to display symptoms; and Tourette's syndrome can be triggered by abnormal metabolism of dopamine. Additional risk factors being investigated include mother drinking alcohol or smoking during pregnancy, birth complications, low birthweight, and infection.
Risk minimization measures	**Routine risk minimization measures:** • SmPC Section 4.4, 4.8 • Patient Leaflet Section 2, 4 **Additional risk minimization measures:** • Educational tool/Material

Important Identified Risk: Depression	
Evidence for linking the risk to the medicine	Cases of depression have been reported in pediatric clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Increased risk for depression in children and adolescents could be associated with being female; a family history of depression, especially in a parent; subclinical depressive symptoms; anxiety; stressful life events; neurobiological dysregulation; temperament (eg, neuroticism); negative conditions; issues with self-regulation and coping; and interpersonal dysfunction. These factors increase the individual's chances of encountering stress and decrease their ability to deal with stress once it occurs (Garber, 2006).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Aggression	
Evidence for linking the risk to the medicine	Cases of aggression/hostility have been reported in clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Rates of certain comorbid psychiatric conditions associated with aggressive behavior are higher in ADHD patients. However, in general, potential risk factors for aggressive behavior in children could include high-conflict, low-cohesive families, high levels of harsh parental discipline, high levels of victimization by peers, and high behavioral inhibition (Watson et al, 2004).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Section 4.4, 4.8 • Patient Leaflet Section 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Drug abuse/Drug dependence	
Evidence for linking the risk to the medicine	Cases of drug abuse/drug dependence have been reported in pediatric clinical trials and the postmarketing setting and are also described in the current prescribing information for CONCERTA.

Risk factors and risk groups	Patients with a history of drug dependence or alcoholism are potentially at risk as these patients may be more likely to abuse this product. Factors that could increase risk of drug use in children and adolescents include early aggressive behavior, lack of parental supervision, substance abuse, drug availability, and poverty; while protective factors could include self-control, parental monitoring, academic competence, anti-drug use policies, and strong neighborhood attachment (National Institute on Drug Abuse, 2003). A meta-analysis suggested that treatment of ADHD disorders with stimulant medications during childhood neither protects nor increases the risk of later substance use disorders (Humphreys et al, 2013), also suggested by a recent study (Molina et al, 2013). With regards to illicit methylphenidate hydrochloride use, there are 5 special populations possibly being high-risk: secondary school students, college students, young adults (not in college), individuals already known to use drugs other than methylphenidate hydrochloride, and individuals with legitimate prescriptions for methylphenidate hydrochloride (Bogle and Smith, 2009).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.1, 4.2, 4.4 • Patient Leaflet Sections 1, 2, 3 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Withdrawal syndrome	
Evidence for linking the risk to the medicine	Cases of withdrawal syndrome have been reported in pediatric clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** • SmPC Section 4.4 • Patient Leaflet Section 2 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Reduced weight gain	
Evidence for linking the risk to the medicine	Cases of reduced weight gain/anorexia have been reported in pediatric clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Data available from CONCERTA clinical trials do not indicate any group is at particular risk for anorexic symptoms, whereas the disease, anorexia nervosa, primarily affects girls/women, even among ADHD children (Curtin et al, 2013).

Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Additional pharmacovigilance activities	• ADDUCE studies
Important Identified Risk: Decreased rate of growth	
Evidence for linking the risk to the medicine	Cases of decreased rate of growth have been reported in the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Many factors affect rate of growth, with genetics playing a prominent role. Short stature is most commonly of genetic determination and correlates well with parental stature. Additional factors for delayed or slower-than-expected growth could include chronic disease, endocrine disorders, emotional health, infection, and poor nutrition (Medline Plus, 2013).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.4, 4.8 • Patient Leaflet Sections 3, 4 **Additional risk minimization measures:** • Educational tool/Material
Additional pharmacovigilance activities	• ADDUCE studies
Important Identified Risk: Seizures	
Evidence for linking the risk to the medicine	Cases of seizure have been reported in the clinical trial and in the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Published literature has different conclusions on the methylphenidate's effect on seizure threshold. Some studies suggest methylphenidate hydrochloride may lower the convulsive threshold in patients with prior history of seizures, in patients with prior electroencephalogram (EEG) abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities.
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Identified Risk: Cerebrovascular disorders	
Evidence for linking the risk to the medicine	Cases of cerebrovascular disorders have been reported in the postmarketing setting, and are also described in the current prescribing information for CONCERTA.

Risk factors and risk groups	Most children presenting with a stroke have an underlying risk factor such as sickle cell disease, or congenital or acquired heart disease. In addition, other risk factors in children could include head and neck infections, systemic conditions such as inflammatory bowel disease and autoimmune disorders, head trauma and dehydration (Roach et al, 2008).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Potential Risk: Suicidality	
Evidence for linking the risk to the medicine	Cases of suicidality have been reported in pediatric clinical trials and the postmarketing setting, and are also described in the current prescribing information for CONCERTA.
Risk factors and risk groups	A review summarized major risk factors for suicide among adolescents: previous suicide attempt, psychiatric disorder/comorbidity, personality disorders, availability of lethal means, impulsive aggression, feelings of hopelessness and worthlessness, family history of depression or suicide, loss of a parent to death or divorce, physical and/or sexual abuse, lack of a social support network, and dealing with homosexuality in an unsupportive family or hostile school environment (Cash and Bridge, 2009).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • Educational tool/Material
Important Potential Risk: Sexual maturation delayed	
Evidence for linking the risk to the medicine	Cases of delayed sexual maturation have been reported in the postmarketing setting.
Risk factors and risk groups	Common causes of delayed sexual maturation include ovarian failure, constitutional delay, psychological and nutritional factors, illicit drugs (such as marijuana), endocrine-related factors (such as thyroid dysfunction, Cushing's syndrome, prolactinomas, congenital adrenal hyperplasias, diabetes mellitus), gonadotropin-releasing hormone deficiency, hypopituitarism, congenital central nervous system defects, benign or malignant pituitary lesions, craniopharyngioma, mullerian agenesis, vaginal septum, imperforate hymen, and androgen insensitivity syndrome (Maharaj, 2012).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2 and 4.4. **Additional risk minimization measures:** • None

Additional pharmacovigilance activities	• ADDUCE studies
Missing Information: Long-term effects	
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.4 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• ADDUCE studies

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of CONCERTA.

II.C.2. Other Studies in Postauthorization Development Plan

ADDUCE studies

Purpose of the study: Marketing Authorization Holders are required to evaluate the publications of the ADDUCE studies to determine if they provide additional pharmacovigilance information for the long-term Missing Information.